10. A dry, moderately cool, mountain atmosphere is most favorable in its influence upon the disease. A hot moist climate, or a damp cold climate are both unfavorable.

11. A nutritous diet of fresh meat and vegetables, warm clothing, exercise in the open air, freedom from exposure to damp and cold, are important elements in the hygienic course of treatment.

12. The care of the skin by frequent hot baths, massage, with inunctions of oils, etc., should receive as much attention as the constitutional treatment.

13. The special remedies which clinical experience would indicate to be of the most value, are chaulmoogra oil, gurjun oil, arsenic, and certain agents of the strychnos family; all are, however, more or less disappointing in their results.

14. All observers agree that in advanced cases, where general dissemination of the bacilli has taken place, curative treatment is absolutely futile. The most favorable conditions are that treatment be instituted early, and that it be prosecuted actively and energetically during a prolonged period.

15. The surgical treatment of leprous sores, necrosed bones, perforating ulcers, the excision of tubercles, amputation of the members, tracheotomy, various delicate operations about the eye, nerve-stretching for the relief of pain, the removal of threatening complications, are of the most signal benefit.

16. Finally, we may conclude that while medical science holds out no definite promise of cure to the leper, its resources are sufficient to arrest or retard the progress of his disease, to promote his comfort, and to prolong his life.

A CLINICAL AND EXPERIMENTAL STUDY OF URÆMIA.

By William E. Hughes, M.D., Ph.D.,
VISITING PHYSICIAN TO THE PHILADELPHIA HOSPITAL; INSTRUCTOR IN PHYSICAL DIAGNOSIS, UNIVERSITY OF PENNSYLVANIA;

AND

William S. Carter, M.D.,
ASSISTANT DEMONSTRATOR OF PATHOLOGY, UNIVERSITY OF PENNSYLVANIA.

(Continued from p. 193.)

Pathogenesis.—At the outset we are confronted by the possibility that uræmia may be due to purely mechanical causes, a theory brought to its highest perfection by Traube, who holds that it is the result of œdema of the brain and consequent anæmia, brought about by the watery condition of the blood, coupled with the increased arterial tension.

Mahommed has further elaborated this by adding a cause for convulsions in numerous punctiform hemorrhages into the gray substance of the brain.

This theory, while it may serve to explain some of the phenomena, most notably localized palsies, can by no means be made to fit into all the facts. Three insuperable difficulties are met with. The conditions under which uræmia arises are so diverse that by no possibility can the same mechanical condition of the brain obtain in all of them. The accumulating evidence of post-mortem examinations negatives the assumed facts. Experimental observations have failed to bear out the theory, so that we are forced to discard this mechanical theory and take refuge in the other, that uræmia is due to substances circulating in the blood. This brings us face to face with another problem: Are these substances constantly present in the blood or do they arise under exceptional circumstances? First, let us consider under what conditions uræmia arises. These may be briefly summarized as (*a*) conditions in which the kidney is diseased and (*b*) those in which its secretion, from other causes, is diminished. We look then naturally to the constituents of the urine for the uræmia-producing substances. Urea, the most important constituent and the one from which the name is derived, cannot be considered the sole, nor, indeed, even the principal, cause. It is not constantly present in excess in the blood of uræmiacs. Uræmia may arise during the free excretion of urea. Experimentally it fails to produce the typical symptoms. Then urea is one of the most powerful diuretics known, and its effect would be rather to relieve than produce uræmia. Carbonate of ammonia, a derivative of urea, brought forward by Frerichs as the cause of uræmia, has greater objections even than urea. It is only exceptionally present in the blood. The injection of large quantities of urea will not be followed by the appearance of carbonate of ammonia. Its formation in the blood presents insuperable difficulties, unless, as was held by Freitz, the conversion of urea into carbonate of ammonia takes place on the gastro-intestinal mucous membrane, whence it is absorbed. But even this would not outweigh the first two facts urged against it.

Landois sprinkled kreatin and kreatinin on the exposed brain centres and got symptoms of uræmia. But our experiments quoted during the consideration of temperature, with the injection of these substances, were negative, no effect whatever being produced. The effect obtained by the local application was evidently due to mechanical or chemical irritation, and kreatin and kreatinin are not uræmia-producers. Thus, then, none of the better known constituents of urine are the ordinary causes of uræmia; and yet urine is distinctly poisonous, as has been determined by Bouchard in his most elaborate series of experiments. He suggests the existence of seven poisons, diuretic (urea), narcotic, sialagogue, myotic, temperature-reducing, and two convulsants, one of which is a potash salt. These poisons, he thinks, are largely alkaloidal. In addition, he determined the fact that the toxicity varies widely, being least during sleep. In some of the specific fevers the toxicity is immensely increased, while in Bright's disease it is diminished.

Laulainé and Chamberlent have shown that toward the end of pregnancy the toxicity is diminished. Favelier found that in children the urine is less toxic than in adults. Feltz and Ritter, who were the first systematic investigators of urinary toxicity, thought the toxic substance was the potash salts; but this Bouchard has disproven. Here we see that while urine is toxic, yet there is a multiplicity of toxic substances, and that their nature is not yet determined. These toxines are probably pre-formed in the blood, for, without limiting its powers merely to filtration, yet it is likely that the office of the kidney is to separate excrementitious substances from the blood and not to create. As the toxicity of the urine varies so appreciably in health, it is probable that disease may still further disturb it, increasing it vastly or even adding new toxines. Hence the possibility of the existence of uræmia without kidney lesion, the result of an over-production of toxic substances. Here let us introduce our experiments upon the production of uræmia:

EXP. XXX.—9.30 A.M. Patient who had been in uræmic condition for several days was bled freely, and the blood whipped with all precautions of antisepsis. This blood was then injected into the jugular vein of a dog weighing 32 pounds, as follows:

11.00 P.M. Dog very lively and in perfect health.

11.15. Injected 10 c.c. per jugular vein.

11.16. Injected 10 c.c. per jugular vein. Urination, defecation, and vomiting. Respiration very irregular, at first slowed, and then later quite rapid.

11.20–11.25. P.M. Injected 30 c.c. Seems very sick.

11.30. Vomiting; heart irregular. Dog will not respond to calling, and makes no effort to get up when untied.

11.40–11.50. Injected 60 c.c. per jugular. Vomiting continuous.

11.55–12.00. Injected 100 c.c. Seems very sick.

12.05 A.M. Injected 150 c.c.

12.30. Condition remains the same. Frequent vomiting and purging. Deeply comatose. Died at 11 A.M. next day.

Autopsy showed brain normal. Lungs contain numerous hemorrhagic infarcts. Heart apparently normal, containing currant-jelly clots. Spleen normal. Liver showed a number of areas much lighter in color than the rest of the organ. Kidneys were both greatly enlarged, cortex swollen, whole organ so hemorrhagic that one cannot make out the pyramids. Blood exudes freely from surface of section on slight pressure. Bladder contained about f℥iij of black urine which contained vast numbers of red blood-cells, blood-casts, and granular matter.

As in this case we had introduced whipped blood containing corpuscles, we made the following control experiment to see the effect of introducing whipped blood from a man without uræmia into a dog.

EXP. XXXI.—Dog, weight 27 pounds. (Bled a case of lead-poisoning.)

12 M. Dog lively. Temp. 39.4° C.

12.20 P.M. Injected 10 c.c. whipped blood per jugular.

12.22. Urination.

12.23.
12.30.
12.33. } Injected 10 c.c. per jugular.
12.34.

Dog untied; runs about the laboratory, and seems as lively as before the injection.

12.45. Injected 30 c.c. per jugular. No effect.

12.57–1.00. Injected 50 c.c. Temperature 39.1° C. As bright and playful as before the injection.

1.15. Injected 30 c.c. per jugular.

1.40–1.50. Injected 75 c.c. per jugular. No effect.

2.00. No symptoms. Urine dark in color. Temperature 39.1° C.

Exp. XXXII.—Same dog as in Experiment XXXI. Weight 30 pounds. The case of lead-poisoning which had been bled for the control Exp. XXXI. developed suppression, only passing two ounces of urine in twenty-four hours. At the end of twenty-four hours, before any uræmic symptoms had appeared, he was bled and the blood allowed to clot. The serum was then injected into the same dog.

1.10 P.M. 100 c.c. blood serum injected slowly into the jugular vein.

1.15. Intense retching; breathing slowly; pupils dilated; comatose..

1.22. Injected 50 c.c. serum into vein.

1.25. In deep coma. When untied makes no effort to get up.

1.30. Respiration rapid.

1.32. Injected 25 c.c. per jugular.

1.45. Remains in deep coma; heart weak; reflexes good. Does not respond to prick of pin.

2.00. In same condition.

2.30. Coma not so deep. Responds to prick of pin, but makes no effort to get up. Urine of normal color.

3.00. Condition the same.

3.12. Had a severe convulsion.

3.22. Died.

Autopsy: Lungs show three or four small hemorrhagic infarcts; liver and spleen normal; kidneys of normal size, slightly congested, especially the pyramids. Bladder contained about f℥j of straw-colored urine which showed nothing on microscopic examination. There was considerable venous congestion of the membranes of the brain, otherwise brain normal.

Exp. XXXIII.—Black dog, weight 13 pounds.

1 P.M. Injected subcutaneously 60 c.c. of blood serum from a case of profound uræmic coma terminating fatally.

1.10. Retching, and vomiting of the contents of the stomach.

1.30. Very dull, seems quite sick.

2.00. Persistent retching; copious vomiting of serous matter.

Placed 60 c.c. of blood serum in a dialyzer with 60 c.c. distilled water. Next day, 1 P. M., injected subcutaneously 60 c.c. of water of dialyzer into same dog. Observed for several hours; no effect. Next day (seventy-two hours after the bleeding) injected the 50 c.c. of blood serum of dialyzer into the same dog without any effect.

Exp. XXXIV.—An old drunkard with long-standing nephritis, cirrhotic liver, and atheromatous arteries was admitted to the hospital with delirium tremens. Urine contained much albumin and hyaline and granular casts. Was passing eight ounces of urine in twenty-four hours, and soon developed uræmic symptoms. Had marked ascites. Was tapped and rapidly improved.

Dog, weight 31 pounds.

2.30 P.M. Temperature 38.8° C.

2.45–2.50. Injected per jugular vein 50 c.c. ascitic fluid.

3 00. No effect.

3.05–3.20. Injected 100 c.c. No effect.

3.50. Injected 200 c.c. Free salivation; retching; very sleepy.

4.00. Retching and vomiting continue.
4.20. Injected 50 c.c. Temperature 39.6° C.
4.30. Injected 75 c.c.
4.50. Very drowsy. Temperature 40.5° C. Urinated very freely. Some vomiting and severe purging continued all the next day.

Exp. XXXV.—Dog, weighing 32 pounds.
2.12 P.M. Temperature 38.3° C.
2.20–2.25. Injected per jugular 50 c.c. ascitic fluid as in Exp. XXXIV.
2.55. Injected 100 c.c. No effect.
3.15. Injected 100 c.c. Seems dull.
3.40–3.45. Injected 100 c.c.
4.00. Vomiting—serous and food ingested. Seems quite ill. Temp. 39.9° C.
4.20. Injected 50 c.c.
4.45. Much sicker. Severe purging. Temp. 39.5° C. Purging and vomiting continued all night and all next day.

Exp. XXXVI.—One week after tapping patient in Exp. XXXIV., the uræmic symptoms had entirely disappeared, but he had ascites again. Was tapped again.
Same dog as in Exp. XXXIV.
3 P.M. Injected 200 c.c. ascitic fluid.
3.15. No effect.
8.20–3.40. Injected 200 c.c.
3.50. Injected 150 c.c. Dog observed for two hours. Does not seem to be affected in any way. No symptoms next day.

Exp. XXXVII.—Same dog as in Exp. XXXV.
2.45 P.M. Injected per jugular 100 c.c. same ascitic fluid as in Exp. XXXVI.
3.00. No effect.
3.15. Injected 100 c.c.
3.45. Injected 150 c.c. No effect at all.

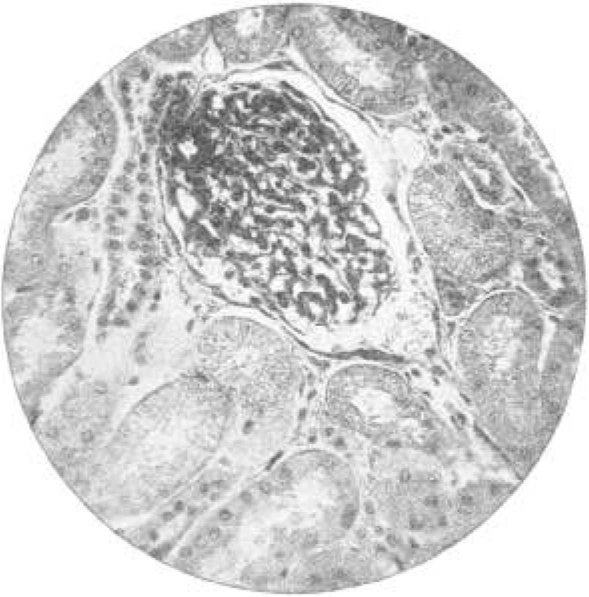
Exp. XXXVIII.—Young dog, weighing 26 pounds. Ligated both renal arteries with all precaution of antisepsis that can be carried out in the laboratory. The operation is not a very severe one, and the animals do not suffer from shock. In some of the experiments both artery and vein were ligated, but usually, as in this experiment, only the renal arteries were ligated. In twenty-four hours the dog seemed very sick, but still walked about. He vomited and purged rather freely. At the end of forty-eight hours it was noticed that he would avoid large objects, but would run against small ones in walking—in other words, he had a central blindness and peripheral vision. His eye-grounds were examined by Dr. James Wallace, who found areas of fatty degeneration in the retina, such as are seen in advanced Bright's disease. There were no hemorrhages and no retinitis.

This dog was then bled to death, and blood allowed to clot. 75 c.c. of the blood serum injected into a dog, weighing 13 pounds, made him quite dull, and he appeared sick (dog had been very lively before).

75 c.c. of the serum, undiluted, was placed in a dialyzer with 75 c.c. of distilled water. The dialyzer was kept in a cool place for twenty-four hours. At the end of this time, 75 c.c. of the distilled water was injected into the same dog, weighing 13 pounds, producing absolutely no symptoms. But the 75 c.c. of blood serum from the dialyzer, injected into the vein of a dog weighing 26 pounds, produced in fifteen minutes severe retching which lasted several hours, and was attended with considerable vomiting.

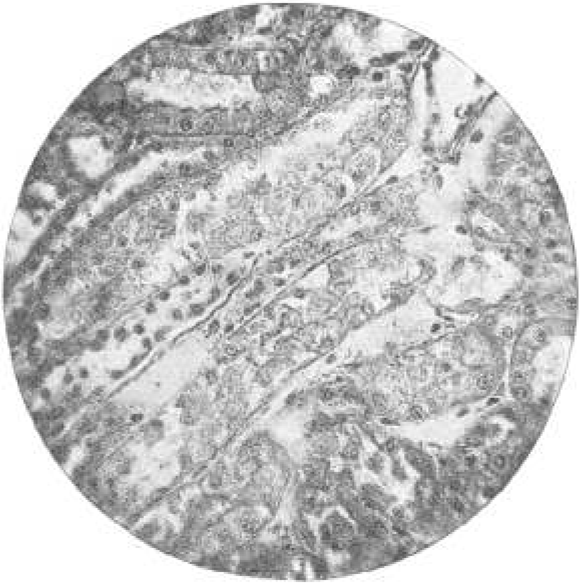
Exp. XXXIX.—Dog, weighing 24 pounds. Ligated both renal arteries. At end of twenty-four hours dog showed great thirst. Drinks water and vomits it immediately. Has been vomiting and purging some little, but is not yet very ill. At the end of forty-eight hours was found in a violent convulsion. Had three convulsions in a half-hour. Was bled to death, but by an accident the blood serum was lost.

FIG. 1.



Convoluted tubules of kidney of dog injected with blood serum of another dog made uræmic by ligation of renal arteries.

FIG. 2.



Collecting tubules of the same kidney.

This was the only case in which we have observed convulsions in the uræmia resulting from ligation of the renal arteries. In several cases we have produced convulsions by the sudden introduction of uræmic serum. The ligation of the renal arteries produces in dogs a condition of uræmia apparently the same as that occurring in man. The symptoms appear in a striking way by the end of twenty-four hours, and death results in from thirty to seventy-two hours. We have produced uræmia in this way in thirteen dogs, some dying before we had the opportunity of bleeding them to death. In the only case in which uræmia did not immediately follow the ligation, there was found an anomaly of two renal arteries to one kidney, and only one had been ligated. The most constant symptoms in these animals are those of the gastro-intestinal tract and the stuporous condition. The blood serum of these animals produces uræmia in other previously healthy animals, just as is produced by the blood serum of men in the condition of uræmia. The following experiments show this.

Exp. XL.—Bled a dog to death ten hours after the ligation of the renal arteries. Blood allowed to clot in the ice-chest. (Of course, in all these experiments the bleeding was done with great care by means of a sterilized glass canula, the blood received in a sterilized flask, and then kept in the ice-chest.)

5.20 p.m. Injected per jugular vein 50 c.c. of this serum into a dog weighing 16.5 pounds.

5.30. Injected 50 c.c.

5.40. Profuse salivation; seems sick; will not stand up when untied.

6.00. Salivation and stuporous condition continue.

In the next four experiments the blood was obtained from three large dogs, twenty-four hours after the ligation of their renal arteries. As they all had the same symptoms (vomiting, purging, and stupor) their blood was mixed and allowed to coagulate.

Exp. XLI.—Dog weighing 28 pounds.

4.45 p.m. Pulse and respiration both slow.

4.50. Injected per jugular 200 c.c. blood serum mentioned above.

4.55. Respiration and pulse remain the same.

4.56. Injected 100 c.c. Muscular tremors; respiration continues slow; pulse very rapid and weak.

5.10. Vomiting.

5.15. Purging; seems very sick. Retching and purging continued several hours.

Exp. XLII.—Dog, weight 26 pounds.

5.15 p.m. Injected 100 c.c. same serum as that used in Exp. XLI. heated to 58° C. for five minutes. No effect from injection.

5.18–5.23. Injected gradually 100 c.c.

5.25. Injected 100 c.c. No effect. When untied runs about room and seems as lively as before the injection.

Exp. XLIII.—Dog, weight 24 pounds.

3.40 p.m. Injected per jugular vein 200 c.c. of serum, obtained as mentioned above, which had been in a dialyzer for thirty-six hours in a cool place, and had been diluted with distilled water before being placed in the dialyzer.

4.00. No effect, except some muscular tremor.

4.10. Some purgation.

Exp. XLIV.—Dog, weight 22 pounds.

4.25 p.m. Injected slowly per jugular vein the distilled water of the dialyzer, 150 c.c. There were no symptoms at any time.

Exp. XLV.—Dog, weight 20 pounds. Large dog, was bled to death twenty-four hours after the ligation of renal arteries.

4.00. P.M. Injected per jugular 75 c.c. of this serum heated to 50° C.
4.30. Free salivation.
4.40. Purging and vomiting.

These gastro-intestinal symptoms continued for some hours. Dog recovered.

EXP. XLVI.—Dog, weight 23 pounds.

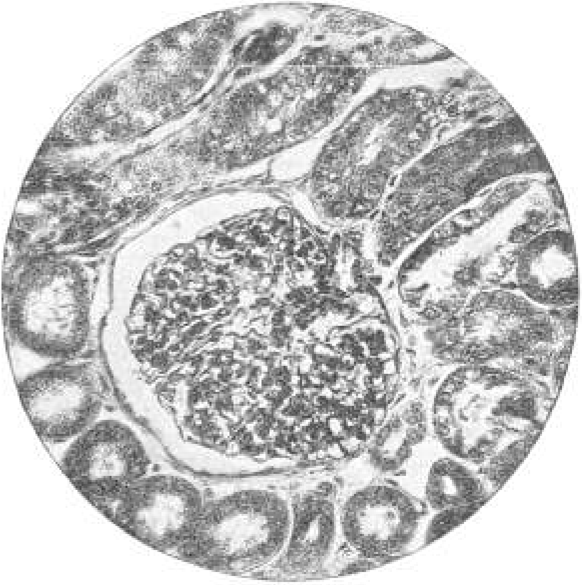
2.33 P.M. Injected per jugular vein 25 c.c. urine of case of subacute Bright's disease. Pulse slowed.
2.34. Injected 50 c.c.
2.35. Injected 100 c.c.
2.36. Injected 50 c.c.
2.38. Injected 100 c.c.

Pulse much slower and pressure lowered after each injection, but it immediately returned to the normal.

2.41. }
2.42. } Injected 50 c.c.
2.43. }
2.45. Injected 75 c.c.
2.57. }
3.00. } Injected 50 c.c.
3.05. }

The respiration became slower and the pulse more frequent in the latter part of the experiment. Notwithstanding the enormous quantity injected the blood-pressure always recovered itself. While the dog did not seem as bright as usual when untied, the only prominent symptom was a profuse diuresis. The dulness lasted several hours and then entirely disappeared.

FIG. 3.

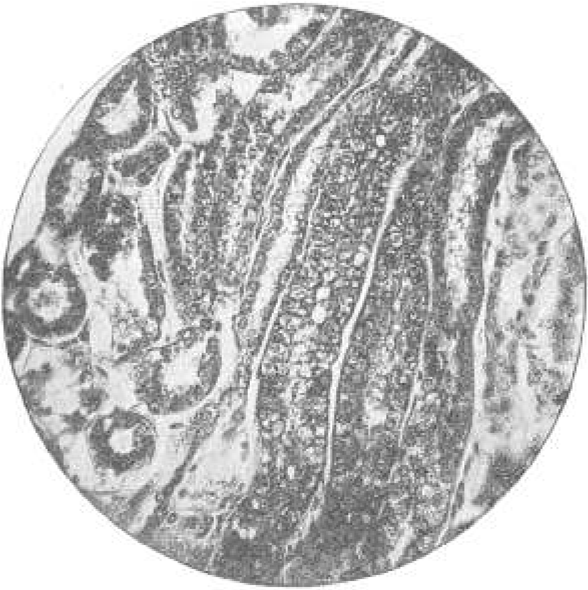


Kidney of dog injected with blood serum of woman having Bright's disease, but without uræmia (Exp. XLVII.). Hardened in Fleming's solution. Showing marked fatty degeneration.

EXP. XLVII.—Bled a woman with chronic parenchymatous nephritis, who had never had any other symptom of uræmia than headache.

Injected 250 c.c. of the blood serum into jugular vein of a dog weighing 25 pounds. There were no symptoms resulting from the injection.

FIG. 4.



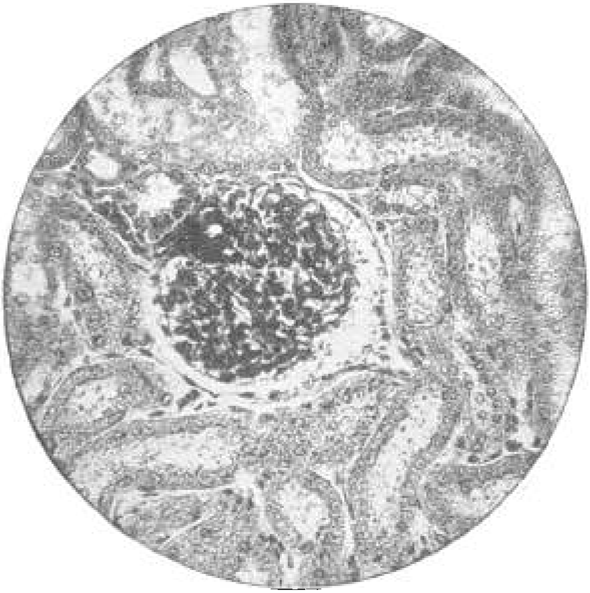
Collecting tubules of same kidney; also showing fatty degeneration.

EXP. XLVIII.—Dog, weight 15 pounds. Injected subcutaneously 50 c.c. blood serum from a case of uræmia, comatose in type. These injections were repeated on each of the three days following. At the seat of each of these injections there was developed an abscess, although the ordinary antiseptic precautions had been taken.

On the fifth day injected per jugular vein 100 c.c. of the serum. The dog became very ill, but did not die. He had showed no positive symptoms until this last injection.

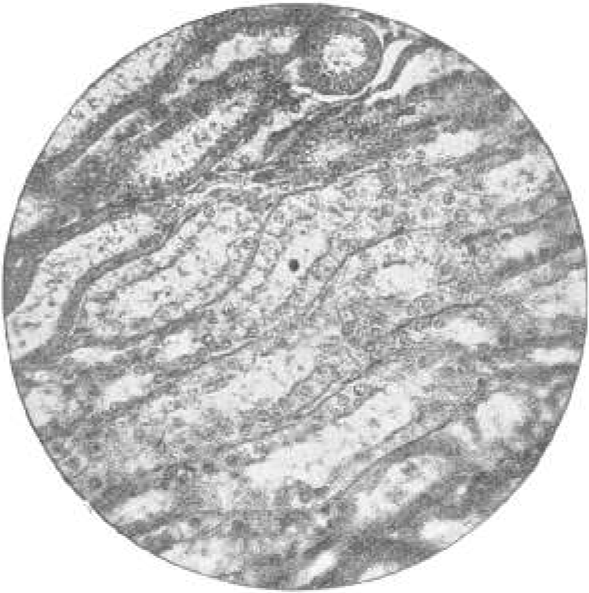
A review of the results of these experiments shows that ligation of the renal arteries in dogs is followed by a progressive fall in blood-pressure and by the constant development of a set of symptoms preceding death, identical in all instances. Serum obtained from the blood of such dogs, or the blood itself injected into other dogs, will produce in these latter a series of exactly similar symptoms, terminating in death if the amount of injecting fluid be large enough. Not only this, but if blood drawn from uræmic human beings be injected, a similar set of phenomena will follow. Or if ascitic fluid obtained during an attack of uræmia be used, the same result will be brought about. If, however, ascitic fluid which has reaccumulated after the uræmia has subsided be used, no such result can be obtained. Whether the fluid is injected subcutaneously or intra-venously makes no difference whatever in the

FIG. 5.



Convoluted tubule of kidney of dog injected with blood serum of man with uræmia.

FIG. 6.



Collecting tubules of same kidney.

state of affairs resulting; the symptoms are exactly similar; possibly they follow somewhat more promptly on an intra-venous injection, but they nowise differ in character or intensity. These symptoms, without going into them in wearisome detail, are those which are referable to the brain and to a condition of the brain which is evidently brought about by the action upon it of some poisonous substance—dulness, coma, loss of muscular power, muscular twitchings or even general convulsions, and disturbances of the gastro-intestinal tract. They are so definite, so uniform, so closely analogous with the symptoms of human uræmia, that it cannot be doubted that we have to deal in them with an artificially produced uræmia. Some of the symptoms developed are worthy of special attention. They are those connected with the gastro-intestinal tract, which in this experimental uræmia are much more uniformly prominent than in human uræmia. Evidently the vomiting and purging, from the character of their onset and their close association with other nervous symptoms, are not altogether an attempt at vicarious elimination, but partly at least centric. Salivation is prominent, differing here from human uræmia, where it is rare.

What is the nature of this uræmia-producing poison? That we have been dealing with one poison, present equally in uræmic human blood, dropsical effusions in uræmia, and in dog's blood in experimental uræmia, is made evident by the perfect similarity of its action. That this poison cannot be one of the ordinarily recognized constituents of the urine, as has been hitherto believed, nor even the sum-total of all these urinary constituents, is proven by the fact which we have demonstrated, that the injection of these constituents or even of urine itself will not produce uræmia; while such injections, if the amount used be inordinately large, will produce certain symptoms, yet these symptoms are not comparable in degree or kind with those produced by the injection of uræmic serum, and they do not constitute the condition which we recognize in man as uræmia. Thus, then, we have in uræmia to deal not with an intoxication due to a retention of urine or its constituents in the blood, but with a poisoning by a substance whose nature, or even, indeed, whose existence, has not yet been recognized. A clinical proof of this same fact is the possibility of the existence of uræmia while in the kidneys there is no demonstrable evidence of disease and normal amounts of normal urine are being secreted. While, however, the retention in the blood of substances ordinarily recognized as being excreted in the urine is not the cause of uræmia, yet after uræmia has been produced, such retention may in all probability have a certain effect, aggravating the already existing condition or determining its variety. The poison, then, must be a special one circulating in the blood under conditions which are not governed wholly by the action of the kidneys as it is evidenced in the urine. As to its exact nature, our experiments have not progressed to the point where we can speak with entire confidence, but further work will undoubtedly clear this up. The facts that we have ascertained positively are that its uræmia-producing power is rendered abortive, or at least much lessened, by the moderate application of heat, and that it is not readily dialyzable. From the foregoing considerations there is at least probability in the assumption that it is some unknown low-grade product of metabolism or any one of a series of such products. From the effect produced upon it by heat and dialysis this seems to be an albuminous body. Clinical facts would seem to indicate that this poison is not constantly circulating in the blood, but that it is only exceptionally present, and that uræmia is induced by its slow and gradual accumulation in the blood, owing to an inability of the kidneys to excrete it, or more rarely to a sudden and enormous production.

Vastly more important even than the bearing of these experiments upon uræmia is their relation to Bright's disease. In the kidneys of dogs injected with uræmic blood serum, or dropsical effusion, there was found a uniform and constant condition. The cells of the tubules, both straight and convoluted, were swollen and granular, the cell walls lost, the nuclei indistinct or breaking down. In places the process had gone so far that the tubules, instead of being lined with a distinct layer of epithelium, were filled with a granular mass in which neither cells nor nuclei could be distinguished, presenting exactly the appearance of a tube-cast *in situ* in common examples of acute nephritis. This granular mass did not take the stain, and the granules failed to clear up on the application of acetic acid, nor did ether dissolve them. As a rule the granules did not take the osmic stain, but occasionally when the lesion was more advanced, owing to the larger amounts of poison employed, they were stained black, showing their fatty nature. Occasionally, too, the endothelium of the Malpighian bodies was proliferating and the tufts beginning to degenerate. Altogether, some of the cases suggested strongly a glomerulo-nephritis as we see it in man. All stages of the lesion could be traced from a beginning granular condition to a decided fatty degeneration; the effect produced upon the kidneys was the same in all instances, the lesions differing only in degree.

In injecting blood serum and urine from cases of Bright's disease where uræmia had not been a symptom, there was no uræmia produced, but there was found after killing the dogs the same lesions of the kidneys as had followed the injection of uræmic fluids. As a rule the lesions were not so marked as in uræmia.

As to the nature of this nephritis-producing substance. From its constant association in large amounts with uræmia it is probably the same as that producing this latter condition. When we obtained the kidney degeneration by injecting serum or urine from Bright's disease, the amounts of injecting fluid used were much larger than in uræmia, so that although the uræmic poison must exist in small proportions here, yet by using larger amounts of the fluid enough of the substance might easily be obtained to affect the kidneys. While moderate heating abated so much of its toxicity as to prevent uræmia, yet it did not prevent nephritis, but the nephritis was not so marked as where heat was not employed. In the dialyzer, when the serum was freely diluted with distilled water, enough of the toxic substance came over to produce nephritis and not uræmia, but, as in heating, the nephritis was here not so marked as before dialyzation.

The demonstration of the existence of this poison, while it explains the origin of at least some of the forms of Bright's disease, explains also many things hitherto obscure as to the connection between uræmia and Bright's disease. If the same poison produces uræmia and nephritis, uræmia would be frequent in acute nephritis—which is a clinical fact—because it must require the presence of large amounts of the poison to produce such marked inflammatory condition of the kidneys, and a nervous system unaccustomed to the presence of the poison must of necessity be profoundly influenced. There being a sudden and probably temporary generation of these large quantities of the poison, it can be easily seen why such uræmia is so frequently recovered from, the poison being soon eliminated, and why such nephritis may completely disappear. Uræmia occurs most frequently during the course of chronic nephritis, not so much on account of a failure of the kidneys to perform their function as because of an unusual generation of the poison, though here probably, when the kidney secretion is blocked, the retention of the constituents of the urine aids in the production of uræmia. Here, too, from the conditions attending the presence of the poison, recovery is frequent. When, on the other hand, uræmia originates slowly at the end of a long-continued nephritis by a slow accumulation of poison, the termination is almost necessarily fatal.

Experiment XLVIII. was very interesting. Here the most marked kidney lesions were obtained, as well as fatty degeneration of the liver. This was the only case in which injection of serum produced abscesses, and this result was evidently connected in some way with an exceptional virulence of the poison, for in bleeding the uræmiac who furnished the serum some of the blood splashing upon the wrist of the operator and the hand of a nurse produced an erythema.

Last, in Experiment XXXVIII., along with the development of the uræmia came the characteristic fatty degeneration of the retina found in Bright's disease. So that albuminuric retinitis, instead of being the result of changes in the retinal vessels, is really due to the direct action of the poison producing uræmia and Bright's disease.

CONCLUSIONS.—1. Uræmia is an intoxication by a poison circulating in the blood.

2. This poison is present in serous effusions as well as in the blood.

3. It is probable that in addition to the pathogenic poison of uræmia there are, under certain conditions, other secondary ones active in its production.

4. The poison producing uræmia will also produce nephritis and a fatty degeneration of the retina, the cause of the eye symptoms in Bright's disease.

5. This poison is probably some albuminous substance. It is affected by heat and is only with difficulty dialyzable.

6. It is probable, but not certain, that this poison is not constantly circulating in the blood, but that under exceptional conditions it becomes developed.

7. It is possible to have uræmia without any previously existing lesion in the kidneys.

TREATMENT.—As uræmia is a poisoned condition of the blood, our efforts should be directed mainly toward the elimination of the poisons. But as their nature is not yet clearly understood, our treatment is still largely empirical, guided and controlled by what little theoretical knowledge we possess.

Convulsions, in addition to the general treatment of uræmia, will sometimes need a treatment of their own. As a rule a convulsion will end spontaneously, but occasionally it will be unduly prolonged, or one may follow another in rapid succession. Here the inhalation of chloroform, ether, or amyl nitrite will be advisable. Of these amyl nitrite is most easily given and is quickest in its action, but it possesses the disadvantage of being less reliable. Morphine in full doses may be used with advantage. While until within a short time its use in Bright's disease has been regarded as extremely dangerous, yet now it is clearly recognized that it is attended with comparatively little risk. Its effect must, however, be carefully watched, for we have unquestionably seen bad results from it. Especially where uræmia complicates fevers must the greatest care be used, for these are the cases in which it is most likely to do harm.

In considering the treatment for general uræmic symptoms, we have to guide us some useful hints derived from the symptoms. First, in those cases in which diarrhœa exists, the nervous symptoms are least likely to be pronounced. Second, the perspiration of uræmiacs frequently contains large quantities of urea.

Following out the first suggestion, then, the bowels are to be kept freely open, or even hypercatharsis produced. Vegetable purgatives have yielded us better results than mineral, besides being easier of administration. If calomel be used, it must be remembered that mercurial salivation is sometimes easily produced in Bright's disease.

Perspiration being the other channel for the elimination of urea, and possibly other excrementitious substances, it must be aided by every means at our command. These are the use of pilocarpine internally and the stimulation of the skin by local measures. Pilocarpine must be exhibited with great care, for its use is not unattended with danger. But recently we have seen a case where pulmonary œdema followed its use, and where a fatal termination was averted only by the most energetic measures. So that free sweating is most safely brought about by external heat, applied either by a hot-air bath or a hot pack. Of the two the hot pack has seemed to us rather preferable, producing less discomfort and exhaustion and being surer in its effect. A number of times we have noted cases in which free perspiration was brought about by a hot pack after a hot-air bath had failed. Outside of hospital practice the hot pack is certainly the more easy of application. Pilocarpine, in small doses, is often a most valuable adjuvant to either the hot-air bath or hot pack.

If there be pyrexia, heat should be most carefully applied, and the temperature constantly watched. If there be any rise such an attempt to produce perspiration must be abandoned. We have seen a case of moderate pyrexia where, owing to a misunderstanding, the patient was left in a hot-air bath for two hours. At the end of that time no perspiration had been induced, but the temperature had risen considerably. After removal from the bath the temperature continued to rise in spite of all efforts to the contrary, and death ensued when it reached 107.9° F.

As the poison is contained in serous effusions as well as in the blood, and as resorption of these effusions may throw enough of the poison into the blood to cause uræmia, it is necessary to withdraw effusions whenever met with, as early as possible. No condition of the patient will contra-indicate tapping. It must be remembered that the symptoms of uræmia are manifold, and that not too much attention must be paid to them from any other point of view than that of uræmia.

Free venesection will abstract directly some of the poison, and, as a treatment, cannot be too highly recommended. Applicable to any form of uræmia, its good effect is most forcibly manifested in the grave cases. The existence of marked dyspnœa is its most urgent indication, and next the presence of prominent cerebral symptoms. It seems, from our experience, that it may abort a threatened attack of uræmia. A pronouncedly weak pulse will in no wise forbid its employment, for we have repeatedly seen the pulse strengthen while the blood was flowing. The quantity to be drawn will depend upon the exigencies of the case and the effect produced, being, as a rule, not less than a pint, or even a quart or more.

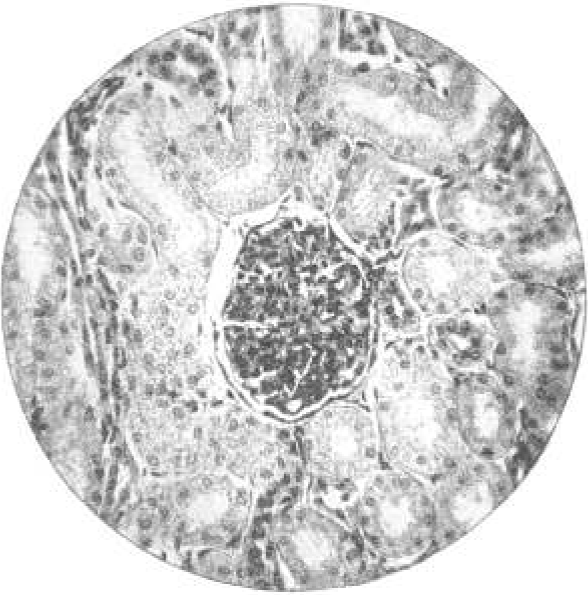
Bloodletting may be beneficially supplemented by transfusion of a normal saline solution. Especially is this valuable where the loss of blood threatens to weaken the heart too much. The saline solution is also diuretic, and may possibly be a direct antidote to the poison. The transfusion may be done intra-venously in exceptional cases when time is of importance; but this may entail some danger unless most carefully performed. Practised subcutaneously, it will be found that absorption is marvellously rapid. We wish to urge strongly this transfusion, for in our hands it has proven of the greatest good. In a case of pulmonary œdema, where its use would be theoretically contra-indicated, it was followed by a most prompt relief of the symptoms, which bloodletting alone failed to abate.

Diuretics are practically of no value. While the cessation of uræmia is attended by a re-establishment of renal secretion, this is a consequence rather than a cause of the cessation, and possibly the attempt to produce artificial diuresis may entail the danger of an additional irritation of an already overloaded kidney.

ADDENDUM.—Since writing the above, which constitutes the Boylston Prize Essay, other experiments have been undertaken which have a direct bearing upon the production of nephritis, and it is thought advisable to insert them here as still further elucidating the subject. In these, serum obtained from the blood of a young man, healthy so far as the kidneys were concerned, was used. The man, aged twenty-two years, was in the Presbyterian Hospital with lumbago. He had had no illness which could have produced a consequent lesion of the kidneys; his urine throughout his stay in the hospital was uniformly normal; nor was there anything in his symptoms or condition which would lead to a suspicion of nephritis. He was bled after his complete recovery from the lumbago. This serum, when injected into dogs, produced no symptoms whatever; but upon killing the dogs lesions of the kidneys were found analogous with those in kidneys where injection of serum from nephritis was practised. The lesions, however, noticed so uniformly throughout the latter, were, where healthy serum was used, not so evenly distributed; in places the kidneys were practically normal, in others slightly degenerated. Nor was the degeneration nearly so pronounced as after the injection of diseased serum; the process seemed to be the same, but it was not so far advanced and there was nowhere any fatty degeneration; in fact, it suggested a smaller amount of poison or one of less virulence. Figs. 7 and 8 show a section through a portion of the kidney most markedly affected.

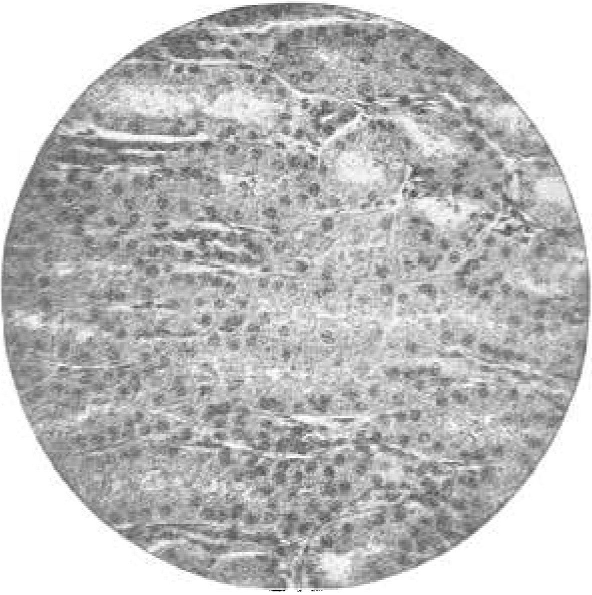
The poison here must be the same as that in the blood of nephritis, for the reason that the lesions obtained in the kidneys are identical. Having established this fact, it is evident that one of two suppositions must be correct—either this man had nephritis or there is constantly

FIG. 7.



Convoluted tubules of kidney of dog injected with blood serum of healthy young man, showing granular appearance of cells.

FIG. 8.



Collecting tubule of same kidney.

present in normal blood a substance which, in sufficient quantities, is capable of producing nephritis. It is scarcely possible that the man's kidneys could have been diseased; great care was taken to exclude this by careful examinations of his urine and by a thorough canvass of his condition and previous diseases; so we are forced to adopt the second supposition, that the nephritis-producing substance is constantly present.

This same serum injected into rabbits produced in their kidneys a degeneration of the same character as that just described in dogs, but very decidedly more violent; the process was quite uniformly distributed and had advanced much farther. The serum of healthy dogs injected into a rabbit produced again the same degeneration, but here less violent than where human serum was used. On the other hand, serum from horses produced no effect upon the kidneys of rabbits.

We have, then, as the result of these experiments the following facts:

1. Healthy human serum will produce in the kidneys of dogs a moderate degeneration and in those of rabbits a degeneration much more violent.

2. Dog's serum will produce in rabbits a degeneration of a moderate degree of intensity.

3. Horse's serum has no effect upon the kidneys of rabbits.

From these facts it is evident that the order in which serums stand as to their toxicity, and so the amounts of toxic substance which they contain, is: human, dog, horse.

This would suggest still further that the origin of this substance is probably to be traced to the character of the food, and that its production takes place somewhere in the digestive system. For the largest amount of poison is found in man, with his meat-ingestion and complex, easily disarranged digestion; next in dogs, with their semi-carnivorous diet; and least in the horse, a pure herbivore. Clinically, it has been well established that cases of Bright's disease improve when meats and kindred substances have been removed from the food, and do best of all upon that simplest of diets, milk. Experimentally it has been shown that the urine of animals is rendered least toxic by a milk diet. These facts would all point in one direction—they refer us to the digestive tract for the origin of the poison.